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FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,918	DAYER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-75* is/are pending in the application.

4a) Of the above claim(s) *1-8, 11-14, 18-35, 44-45, and 50-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,15,16,36-43,46-49 and 62-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-16 and 18-75 are pending.

2. Claims 1-8, 11-14, 18-35, 44-45, and 50-61 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 9-10, 15-16, 36-43, 46-49 and 62-74 are being acted upon in this Office Action.

4. In view of the amendment filed 7/24/06, the following rejections remain.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 9-10, 15-16, 36-43, 46-49 and 62-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for

(1) A process for making an apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment comprising culturing a eukaryotic cell comprising a vector comprising a nucleic acid molecule consisting of the nucleotide sequence selected from the group consisting of: (a) the nucleotide sequence as set forth in residues 73 to 601 in SEQ ID NO: 1; (b) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO: 2; (c) the nucleotide sequence as set forth in residues 73 to 451 in SEQ ID NO:1; (d) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO:2; (e) the nucleotide sequence as set forth in residues 485 to 820 in SEQ ID NO:1 ; (f) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ I D NO:2; (g) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO:2; (h) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO:2 wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin-1 (IL-1) production by monocytes; wherein a culture condition suitable for expressing the polypeptide is selected and the polypeptide is isolated from the culture;

(2) A process for making an apo-A-l fragment T-cell activation inhibitor-like polypeptide fragment comprising culturing a prokaryotic cell comprising a vector comprising a nucleic acid molecule consisting of the nucleotide sequence selected from the group consisting of: (a) the nucleotide sequence as set forth in residues 73 to 601 in SEQ ID NO: 1; (b) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO: 2; (c) the nucleotide sequence as set forth in residues 73 to 451 in SEQ ID NO:1; (d) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO22; (e) the nucleotide sequence as set forth in residues 485 to 820 in SEQ l D NO:1; (f) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 11 3 in SEQ ID NO:2; (g) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO:2; (h) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO:2 wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin-1 (IL-1) production by monocytes; wherein a culture condition suitable for expressing the polypeptide is selected and the polypeptide is isolated from the culture;

(3) An isolated apo-A-l fragment T-cell activation inhibitor-like polypeptide fragment consisting of the amino acid sequence selected from the group consisting of: (a) an amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) an amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO: 2; (e) an amino acid sequence as set forth in residues 73 to 113 of SEQ ID NO: 2 and wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin-l (IL-1) production by monocytes;

(4) An isolated apo-A-l fragment T-cell activation inhibitor-like polypeptide fragment encoded by a nucleic acid molecule consisting of the nucleotide sequence selected from: (1) the nucleotide sequence as set forth in residues 73 to 601 in SEQ ID NO: 1; (2) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO: 2; (3) the nucleotide sequence as set forth in residues 73 to 451 in SEQ ID NO: 1; (4) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO:2; (5) the nucleotide sequence as set forth in residues 485 to 820 in SEQ ID NO: 1; (6) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ ID NO: 2; (7) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO: 2; (8) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO: 2 wherein

the nucleotide sequence encodes a polypeptide that inhibits tumor necrosis factor (TNF) or interleukin-l (IL-1) production by monocytes;

(5) A composition comprising the polypeptide mentioned above and a pharmaceutically acceptable formulation agent;

(6) A composition comprising the polypeptide mentioned above and a pharmaceutically acceptable formulation agent wherein the pharmaceutically acceptable formulation agent comprises at least one of a carrier, adjuvant, solubilizer, stabilizer, or anti-oxidant;

(7) The isolated mentioned above which is covalently modified with a water-soluble polymer;

(8) The isolated polypeptide mentioned above wherein the water-soluble polymer is selected from polyethylene glycol, monomethoxy-polyethylene glycol, dextran, cellulose, poly-tN-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols, and polyvinyl alcohol;

(9) A fusion polypeptide comprising the isolated apo-A-l fragment T-cell activation inhibitor-like polypeptide fragment mentioned above and a heterologous amino acid sequence selected from an IgG constant domain or fragment thereof, an alkaline phosphatase or a fragment thereof, a tat protein, or a FLAG epitope and

(10) The fusion polypeptide mentioned above and a heterologous amino acid sequence wherein the heterologous amino acid sequence is an IgG constant domain for detection assays. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Enablement is not commensurate in scope with claims as how to make and use (1) any T-cell activation inhibitor polypeptide fragment of apo-A-1 having at least 85%, 90% or 95%

identity to the amino acid sequence encoded by the nucleotide sequence of any one of (a) - (h) as set forth in claim 9(i), 64, and 65, respectively (2) any T-cell activation inhibitor polypeptide fragment of apo-A-1 having at least 85%, 90% or 95% identity to the amino acid sequence as set forth in claim 68, 69, 72 and 73 and (3) any T-cell activation inhibitor polypeptide fragment of apo-A-1 wherein the fragment is at least 75 amino acids shorter than SEQ ID NO: 2 as set forth in claim 66 and 74 wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin 1 (IL1) production by monocytes for treating any IL-1 mediated diseases such as ALS, Alzheimer's disease and others diseases listed on page 66-68 and any TNFα mediated disease such as cancer, cachexia/anorexia, depression and other diseases listed on pages 69-70 of the specification.

The specification discloses only human Apo-A-I comprising SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. The only human Apo-A1 fragment recovering from the fractions 23-26 with a molecular weight 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 has inhibitory activity of T cell signaling of monocyte for IL-1β and TNFα production in vitro (See p7, Figure 4A-B). The term conservative amino acid substitution" as defined in the specification at page 25 is any substitution of a native amino acid residue with a nonnative residue, including non-naturally occurring amino acid residues exemplified in Table 1.

The specification does not teach which nucleic acid residues, the corresponding amino acids residues within the nucleic acid sequence as set forth in residues 73 to 601, 73 to 451, 485 to 820 in SEQ ID NO: 1 or nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194, 25 to 144, or 25 to 113 in SEQ ID NO: 2 are critical and can or cannot be change such as substitution, deletion, addition and combination thereof such that the resulting fragment of apo-A-I having at least 85%, 90% or 95% sequence identity to said nucleic acid or amino acid sequence still maintains its structure and function. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo.

There is no disclosure of any apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) having more than one conservative amino acid substitutions, much less the radically different polypeptides having no resemblance to amino acid residues 25 to 194 of SEQ ID NO: 2 still maintain structure and functions. Therefore, the only isolated apo-A-l fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) that are enabled are those consisting of the amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) an amino acid

sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO:2; (e) an amino acid sequence as set forth in residues 73 to 1 13 of SEQ ID NO22, the corresponding polynucleotide encoding said polypeptides.

A sequence with at least 85% sequence identity to amino acid residues 25 to 194 in SEQ ID NO: 2 means there are at least 15% differences, which is equivalent to 18 amino acids differences. The specification as filed does not teach which amino acids within residues 25 to 194 in SEQ ID NO: 2 to be modified by addition, deletion, substitution such that the modified apo-Ai fragment still inhibits tumor necrosis factor or interleukin-1 production by monocytes, let alone it could treat any diseases such as ALS, Alzheimer's disease and cancer. There is a lack of in vivo working example demonstrating the claimed T-cell activation inhibitor polypeptide fragment of apo-A-I could treat any and all disease. It is not predictable which undisclosed apo-A-I fragment that is at least 50 amino acids shorter than SEQ ID NO: 2 having various amino acid substitution, deletion, addition that resulted in merely 85% or 90% sequence identity still inhibits tumor necrosis factor production or interleukin-1 (IL-1) production, or T cell activation in vitro. The intended use of the Apo-A-I fragment is for treating any and all IL-1 and/or TNF mediated diseases. However, there are no working examples of such (AFTI) polypeptide fragment could any disease.

Dermer et al teach that "Petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapt to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference teaches that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interaction.

Gura et al teach the shortcomings of potential anti-cancer agents including extrapolating from in vitro protocols, the problems of drug testing for cancer is that the model system are not predictive at all.

Attwood *et al*, of record, teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable.

Skolnick *et al*, of record, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular). While it is known in the art how to make amino acid substitution in polypeptide, such polypeptide is not predictable of their being able to inhibit TNF or IL-1 production in vivo or T cell activation. Therefore, it would require undue experimentation to determine how to practice the invention as it is drawn to any apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) having no resemblance to the residues 25 to 194 of SEQ ID NO: 2, the corresponding polynucleotide other than those specific nucleic acid sequences consisting of the (nucleotides 73 to 582, 73 to 432, 466 to 801 in SEQ ID NO: 1) and amino acid sequences consisting of the (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2). Given the unlimited number of apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment having one or more substitutions, the radically different polypeptides would obviously be inoperable. Accordingly, an undue experimentation would be required to determine how to practice the claimed invention.

In addition to the problems mentioned above, there is insufficient guidance as to the structure of any AFTI-like polypeptide without the nucleotide sequence or the amino acid sequence. The term "comprising" or "having" is open-ended. It expands fragment of amino acid sequences from (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2) to include additional amino acids at either or both ends. There is insufficient guidance as to which amino acids, the corresponding nucleotides to be added and whether the resulting AFTI-like polypeptide fragments maintain its structure and functions.

The specification does not teach which amino acids within the full-length sequence of human Apo-A-I polypeptide (AFTI) are critical and can or cannot be change such as substitution, deletion, addition and combination thereof. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo.

The specification discloses only nucleic acid consisting of (nucleotides 73 to 601, 73 to 451, 485 to 820 in SEQ ID NO: 1) encoding the Apo-I fragment and the amino acid sequences consisting of (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2) that inhibits TNF or IL-1 production by monocytes in vitro.

There is no disclosure of any apo-A-I polypeptide fragment at least 75 amino acids shorter than SEQ ID NO: 2 other than the specific fragments mentioned above that inhibits TNF or IL-1 production by monocytes in vitro. The term "at least" has no upper limited as to how short the apo-A-I fragment could be and still maintains its structure and function (claims 66 and 74).

The state of the art with respect to the issue of structure-function relationship on the ability of apo-A1 to suppress TNF alpha/IL-1 production by monocytes and/or T cell activation is not well understood but may appear that the inhibitory effect of apo-A-1 via T-cell signaling since contact between monocytes and activated T cells was required (see Hyka et al, Immunobiology 97(8): 2381-2389, April 2001, PTO 892; page 2386-87, in particular). The specification provides no guidance as to other apo-A-I polypeptide variants from human or other species having the same functions as the specific apo-A1 fragment for inhibiting TNF alpha/IL-1 production by monocytes. As such, an undue amount of experimentation would be required to determine how to practice the claimed invention. Given that the interaction between Apo-I polypeptide fragments and monocytes has not been characterized, it would require undue experimentation to determine how to make functional Apo-A1 fragment as broadly as claimed. Since the structures associated with function of any of the apop-A-fragment T-cell activation inhibitor-like polypeptides mentioned above are not enabled, it follows that any composition comprising said polypeptides are not enabled. It also follows that any apop-A-fragment T-cell activation inhibitor-like polypeptides mentioned above covalently modified and any fusion protein comprising said polypeptide are not enabled.

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/24/06 have been fully considered but are not found persuasive.

Applicants' position is that the amino acid "substitution, deletion" etc. language has been removed from the claims and the claims have been newly formulated with amino acid "identity" language specifically found acceptable in the PTO guidelines and recent Board of Appeals case laws.

In response, the cited Capon case law and PTO guidelines Example 14 by applicants address the issue of written description. It is noted that this rejection is about enablement, not written description. Although the claims have been amended to recite sequence identity, the specification discloses only human Apo-A-I comprising SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. The only human Apo-A1 fragment recovering from the fractions 23-26 with a molecular weight 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 has inhibitory activity of T cell signaling of monocyte for IL-1β and TNFα production in vitro (See p7, Figure 4A-B). The term conservative amino acid substitution" as defined in the specification at page 25 is any substitution of a native amino acid residue with a nonnative residue, including non-naturally occurring amino acid residues exemplified in Table 1.

The specification does not teach which nucleic acid residues, the corresponding amino acids residues within the nucleic acid sequence as set forth in residues 73 to 601, 73 to 451, 485 to 820 in SEQ ID NO: 1 or nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194, 25 to 144, or 25 to 113 in SEQ ID NO: 2 are critical and can or cannot be change such as substitution, deletion, addition and combination thereof such that the resulting fragment of apo-A-I having at least 85%, 90% or 95% sequence identity to said nucleic acid or amino acid sequence still maintains its structure and function. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo.

There is no disclosure of any apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) having more than one conservative amino acid substitutions, much less the radically different polypeptides having no resemblance to amino acid residues 25 to 194 of SEQ ID NO: 2 still maintain structure and functions. Therefore, the only isolated apo-A-l fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) that are enabled are those consisting of the amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) an amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO:2; (e) an amino acid sequence as set forth in residues 73 to 1 13 of SEQ ID NO22, the corresponding polynucleotide encoding said polypeptides.

A sequence with at least 85% sequence identity to amino acid residues 25 to 194 in SEQ ID NO: 2 means there are at least 15% differences, which is equivalent to 18 amino acids differences. The specification as filed does not teach which amino acids within residues 25 to 194 in SEQ ID NO: 2 to be modified by addition, deletion, substitution such that the modified apo-Ai fragment still inhibits tumor necrosis factor or interleukin-1 production by monocytes, let alone it could treat any diseases such as ALS, Alzheimer's disease and cancer. There is a lack of in vivo working example demonstrating the claimed T-cell activation inhibitor polypeptide fragment of apo-A-I could treat any and all disease. It is not predictable which undisclosed apo-A-I fragment that is at least 50 amino acids shorter than SEQ ID NO: 2 having various amino acid substitution, deletion, addition that resulted in merely 85% or 90% sequence identity still inhibits tumor necrosis factor production or interleukin-1 (IL-1) production, or T cell activation in vitro. The intended use of the Apo-A-I fragment is for treating any and all IL-1 and/or TNF mediated diseases. However, there are no working examples of such (AFTI) polypeptide fragment could any disease.

With regard to claims 66, 70 and 74, there is no disclosure of any apo-A-I polypeptide fragment at least 75 amino acids shorter than SEQ ID NO: 2, other than the specific fragments mentioned above, inhibits TNF or IL-1 production by monocytes in vitro. The term "at least" has no upper limit as to how short the apo-A-I fragment could be and still maintains its structure and function, in turn, effective for treating any diseases. Accordingly, an undue experimentation would be required to determine how to practice the claimed invention.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 9, 15, 36, 66-67 and 74 are rejected under 35 U.S.C. 102(b) as being anticipated by 5,408,038 (of record, issued April 18, 1995; PTO 892).

The '038 patent teaches an isolated polypeptide apo-A-I comprising the amino acid sequence that is 100% identical to the claimed SEQ ID NO: 2 (see reference SEQ ID NO: 3, Fig 2, in particular). The reference polypeptide of SEQ ID NO: 3 encompass the claimed polypeptide fragment "comprising" an amino acid residues (residues 25 to 194, 25 to 144, 25 to 113, 73 to

113 and 156 to 267 in SEQ ID NO: 2). The term "comprising" or "having" is open-ended. It expands the claimed fragment to include additional amino acids at either or both ends to include the reference polypeptide. Given that the reference polypeptide has the same structure as the claimed apo-A-I polypeptide, the reference polypeptide inherently has the same properties such as inhibition of tumor necrosis or interleukin-1 (IL-1) production by monocytes. The '038 patent teaches one or more conservative amino acid substitutions (see col. 10, lines 1 to 40, col. 19, line 65-68 bridging col. 20, lines 1-11, in particular). The '038 patent also teaches a nucleic acid comprising SED ID NO: 4 that encodes the claimed apo-A-I polypeptide of SEQ ID NO: 2. The reference nucleotide sequence of SEQ ID NO: 4 includes the claimed (nucleotides 73 to 582, 73 to 432, 466 to 801 in claimed SEQ ID NO: 1). The '038 patent further teaches a process of making the reference polypeptide comprising culturing a eukaryotic cell comprising vector having the DNA encoding the reference polypeptide (see col. 31, lines 45-58, col. 30, lines 21-26, in particular). The '038 patent further teaches a fusion protein comprising the reference apo A-I polypeptide from residue 19 through residue 240 fused to a heterologous amino acid sequence such as β-galactosidase (see col. 18, lines 22-25, claim 12 of the '038 patent in particular). The '038 patent also teaches a composition comprising the reference apo-A-I polypeptide and a carrier such as phosphate-buffered saline or solubilizer such as triton X-100 (see col. 12, lines 62-67, in particular). The '038 patent further teaches a plasmid encoding an apo-A-I polypeptide fragment from amino acid residues 120 to 135 of the reference SEQ ID NO: 3 and method of making the same (see Recombinant DNA molecule, reference SEQ ID NO: 5, in particular); the reference polypeptide fragment is at least 50 or 75 amino acids shorter than the claimed SEQ ID NO: 2 since the reference is only 15 amino acid in length from the full-length sequence of SEQ ID NO: 3 (see reference SEQ ID NO: 5, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 7/24/06 have been fully considered but are not found persuasive.

Applicants' position is that in light of the amendments to the claims which now limits the claims to polypeptides of about 217 amino acids or less or about 182 amino acids or less or to the specific polypeptide fragments, it is submitted that the '038 patent is no longer relevant.

In response, the terms "comprising" in claim 15 and "having" in claim 67 open-ended. It expands the claimed fragment to include additional amino acids at either or both ends to include the reference polypeptide. Further, the '038 patent further teaches a plasmid encoding an apo-A-I

polypeptide fragment from amino acid residues 120 to 135 of the reference SEQ ID NO: 3 (see Recombinant DNA molecule, reference SEQ ID NO: 5, in particular), the reference polypeptide fragment is at least 50 or 75 amino acids shorter than the claimed SEQ ID NO: 2 since the reference is only 15 amino acid in length from the full-length sequence of SEQ ID NO: 3 (see reference SEQ ID NO: 5, in particular).

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 15 and 36-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,408,038 (of record, issued April 18, 1995; PTO 892) in view of US Pat No. 5,824,784 (Oct 1998; PTO 892) and/or US Pat No. 5,876,968 (issued March 2, 1999; PTO 892).

The teachings of the '038 patent have been discussed supra. The '038 patent teaches apoA-I is unstable (see column 2, lines 6-8, in particular). The '038 patent teaches the reference apo-A-I is useful for diagnostic assays for determining HDL and LDL levels in body fluid sample (see abstract, in particular).

The claimed invention in claims 38, and 39 differs from the teachings of the reference only in that composition wherein the pharmaceutically acceptable formulation agent comprises at least one of adjuvant, stabilizer or anti-oxidant.

The claimed invention as recited in claims 40 and 42 differs from the teachings of the reference only in that polypeptide is covalently modified with a water-soluble polymer.

The claimed invention as recited in claims 41 and 43 differs from the teachings of the reference only in that polypeptide is covalently modified with a water soluble polymer wherein the water soluble polymer is selected from polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol.

The '784 patent teaches method and composition for covalently modified any polypeptide of interest such as G-CSF or INF with a water-soluble polymer such as polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol (See abstract, column 6, lines 32-67 bridging column 7, lines 1-5, column 9, lines 64-66, in particular). The '784 patent further teaches pharmaceutically acceptable formulation agent such as carrier such as phosphate buffer, adjuvant, solubilizer such as Tween 80, anti-oxidants such as ascorbic acid, and sodium metafisulfate (See column 11, lines 11-32, in particular). The advantages of N-terminally pegsylated protein are that it provides a homogeneous preparation to ease in clinical application, with predictability of lot to lot pharmacokinetics for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

The '968 patent teaches a pharmaceutical composition comprising human Apo A1-M together with a stabilizing agent such as phospholipids and/or a carrier (see paragraph bridging col. 3 and col. 4, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently modified the apo-A-I polypeptide as taught by the '038 patent to the water soluble polymer as taught by the '784 patent and formulates the composition in pharmaceutically acceptable carrier such as phosphate buffer, solubilizer such as Tween 80 or stabilizer or antioxidant as taught by the '784 patent and/or the phospholipids stabilizer as taught by the '968 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '038 patent teaches that apoA-I is unstable (see column 2, lines 6-8, in particular) and the apo-A-I

polypeptide is useful for diagnostic assays for determining HDL and LDL levels in body fluid sample (see abstract, in particular). The advantages of N-terminally pegsylated protein are that it provides a homogeneous preparation to ease in clinical application, with predictability of lot to lot pharmacokinetics for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity as taught by the '784 patent (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular). The '968 patent teaches a pharmaceutical composition comprising human Apo A1-M together with a stabilizing agent such as phospholipids and/or a carrier (see paragraph bridging col. 3 and col. 4, in particular).

Applicants' arguments filed 7/24/06 have been fully considered but are not found persuasive.

Applicants' position is that in light of the amendments to the claims which now limits the claims to polypeptides of about 217 amino acids or less or about 182 amino acids or less or to the specific polypeptide fragments, it is submitted that the '038 patent is no longer relevant.

In response, the terms "comprising" in claim 15 and "having" in claim 67 open-ended. It expands the claimed fragment to include additional amino acids at either or both ends to include the reference polypeptide.

12. Claims 15 and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,408,038 (of record, issued April 18, 1995; PTO 892) in view of US Pat 5,116,964 (of record, May 1992; PTO 892).

The teachings of the '038 patent have been discussed supra. The '038 patent further teaches a fusion protein comprising the reference apo A-I polypeptide from residue 19 through residue 240 fused to a heterologous amino acid sequence such as β-galactosidase (see col. 18, lines 22-25, claim 12 of the '038 patent in particular). The '038 patent teaches the reference apo-A-I is useful for diagnostic assays for determining HDL and LDL levels in body fluid sample (see abstract, in particular).

The claimed invention as recited in claims 46-49 differs from the teachings of the reference only that the fusion polypeptide comprising an isolated apo-A-I T cell activation inhibitor-like polypeptide fragment consisting essentially of an amino acid sequence as set forth in (a) to (e) having one or more conservative amino acid substitutions fused to an IgG constant or fragment thereof instead of β-galactosidase.

The '964 patent teaches immunoglobulin fusion polypeptide comprising a fragment of immunoglobulin such as CH2 and CH3 domains of the constant region of an immunoglobulin or the Fc fused to any polypeptide of interest such as LHR (See abstract, column 10, lines 10-16, in particular). The advantage of immunoglobulin fusion polypeptide is that it extends the half-lives of the fusion protein and is useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the β-galactosidase in the fusion protein comprising apo A-I polypeptide fused to β-galactosidase as taught by the '038 patent for the CH2 and CH3 domains of the constant region of an immunoglobulin or the Fc as taught by the '964 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '038 patent teaches that apoA-I is unstable (see column 2, lines 6-8, in particular) and the '964 patent teaches immunoglobulin fusion polypeptide extends the half-lives of the fusion protein (See column 8, lines 10-34, in particular).

Applicants' arguments filed 7/24/06 have been fully considered but are not found persuasive.

Applicants' position is that in light of the amendments to the claims which now limits the claims to polypeptides of about 217 amino acids or less or about 182 amino acids or less or to the specific polypeptide fragments, it is submitted that the '038 patent is no longer relevant.

In response, the terms "comprising" in claim 15 and "having" in claim 67 open-ended. It expands the claimed fragment to include additional amino acids at either or both ends to include the reference polypeptide.

13. Claims 15, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,408,038 (of record, issued April 18, 1995; PTO 892) in view of Schwarze et al (Science 285(3): 1569-1572, Sept 1999; PTO 892) or US Pat No 5,789,655 (issued Aug 4, 1998; PTO 892) or Kershbaumer et al (Immunotechnology 2(2): 145-50, June 1996; PTO 892).

The teachings of the '038 patent have been discussed supra. The '038 patent further teaches a fusion protein comprising the reference apo A-I polypeptide from residue 19 through residue 240 fused to a heterologous amino acid sequence such as β-galactosidase (see col. 18,

lines 22-25, claim 12 of the '038 patent in particular). The '038 patent teaches the reference apo-A-I is useful for diagnostic assays for determining HDL and LDL levels in body fluid sample (see abstract, in particular).

The claimed invention as recited in claims 46 and 48 differs from the teachings of the reference only in that the fusion polypeptide wherein the heterologous amino acid sequence is an alkaline phosphatase, a tat protein, or a FLAG epitope.

Schwarze et al teach a fusion protein comprising a tat protein containing an NH-2 terminal 11 amino acid protein transduction domain (PTD) fused to β-gal (see page 1569 to 1570, Fig 2A, in particular) or FITC (see page 1570, in particular). Schwarze et al teach the tat protein in the fusion protein is useful for delivering the fusion protein inside the cells of the patients in the context of protein therapy (see page 1571, col. 1, abstract, in particular).

The '655 patent teaches various epitope sequences such as FLAG epitope that are useful for tagging and detecting recombinant proteins (see col. 11, lines 50-67, col. 12, lines 1-9, in particular). The '655 patent teaches inclusion of the FLAG epitope in the recombinant fusion proteins avoids the necessity for the development of a specialized scheme or functional assays for protein purification (se col. 12, lines 5-10, in particular).

Kershbaumer et al teach alkaline phosphatase fusion proteins comprising single chain Fv fragments fused to the N-terminus of alkaline phosphatase from E coli (see abstract, in particular). The fusion protein is useful in single step purification via metal affinity chromatography for various assays such as ELISA and immunowestern blotting (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the β-galactosidase in the fusion protein comprising apo A-I polypeptide having one or more conservative amino acid substitution fused to β-galactosidase as taught by the '038 patent for the tat protein that deliver the protein inside the cell as taught by Schwarze or the FLAG epitope as taught by the '655 patent, or the alkaline phosphatase as taught by Kershbaumer et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '038 patent teaches the reference apo-A-I is useful for diagnostic assays for determining HDL and LDL levels in body fluid sample (see abstract, in particular). Schwarze et al teach the tat protein

in the fusion protein is useful for delivering the fusion protein inside the cells in the context of protein therapy (see page 1571, col. 1, abstract, in particular). The '655 patent teaches FLAG epitope fusion protein is useful for tagging and detecting recombinant proteins and avoids the necessity for the development of a specialized scheme or functional assays for protein purification (se col. 12, lines 5-10, in particular). Kershbaumer et al teach alkaline phosphatase in the fusion protein is useful in single step purification via metal affinity chromatography for various assays such as ELISA and immunowestern blotting (see abstract, in particular).

Applicants' arguments filed 7/24/06 have been fully considered but are not found persuasive.

Applicants' position is that in light of the amendments to the claims which now limits the claims to polypeptides of about 217 amino acids or less or about 182 amino acids or less or to the specific polypeptide fragments, it is submitted that the '038 patent is no longer relevant.

In response, the terms "comprising" in claim 15 and "having" in claim 67 open-ended. It expands the claimed fragment to include additional amino acids at either or both ends to include the reference polypeptide.

14. The following new grounds of rejection are necessitated by the amendment filed 7/24/06.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 9-10, 15-16, 36-43, 46-49 and 62-74 are rejected under 35 U.S.C. 1 12, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The term "at least 50 amino acids shorter than" in claims 9, 15 and 16 represents a departure from the specification and the claims as originally fled. The passages pointed out by applicant in the amendment filed 7/24/06 do not provide a clear support for the said phrase.

The term "at least 75 amino acids shorter than" in claim 65, 70 and 75 represents a departure from the specification and the claims as originally fled. The passages pointed out by applicant in the amendment filed 7/24/06 do not provide a clear support for the said phrase.

The term "residues 73 to **582** in SEQ ID NO: 1" in claims 9(a) and 16(1) represents a departure from the specification and the claims as originally fled. It would be helpful if applicants point out the support for said residues.

The term "residues **73 to 432** in SEQ ID NO: 1" in claim 9(c) and 16(3) represents a departure from the specification and the claims as originally fled. It would be helpful if applicants point out the support for said residues.

The term "residues **466** to **801** in SEQ ID NO: 1" in claims 9(e) and 16(5) represents a departure from the specification and the claims as originally fled. It would be helpful if applicants point out the support for said residues. The specification and the claims as originally filed discloses the nucleic acid sequence as set forth in residues 73 to 601, 73 to 451, 485 to 820 in SEQ ID NO: 1, see summary of invention.

The term "at least 75 amino acids shorter than" in claims 66, 70 and 74 represents a departure from the specification and the claims as originally fled. The passages pointed out by applicant in the amendment filed 7/24/06 do not provide a clear support for the said phrase.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

18. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "the amino acid sequence of any one of (2) – (9)" in amended claim 16 (9) has no antecedent basis in any one of (2) to (9) because the word "amino acid sequence" is not recited in claim 9 (3) and claim 9 (5). The sequences in claim 9 (3), (5) are nucleotide sequences.

19. No claim is allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

22. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
October 13, 2006

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600